Reining in EGF

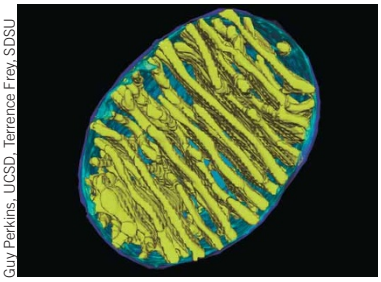
By combining a cell-based vaccine with monoclonal antibodies, cancer researchers have blasted tumors overexpressing the HER-2/neu receptor in mice. The mice are a model for human cancers—including pancreatic, lung, ovarian and 30% of breast carcinomas—which overexpress this member of the epidermal growth factor receptor family.

The monoclonal antibody-based drug Herceptin (trastuzumab) can help some breast cancer patients with excess HER-2/neu and was heralded as one of the first of targeted cancer therapies in the late 1990's. But not all of these patients respond to the drug.

In the 15 August issue of *Journal of Immunology*, Wolpoe *et al.* infused mice with two different monoclonal antibodies to HER-2/neu, along with a cell-based vaccine. The approach prevented tumors in 70% of HER-2/neu–overexpressing mice and eradicated tumors in 30%. The success rate was higher than in experiments using either antibodies or vaccination alone, or in experiments using just one monoclonal antibody with vaccination.

The new study comes on the heels of others showing some efficacy in mice treated with cell-based vaccines against HER-2/neu. Other groups have isolated neu-specific T cells and antibodies from the blood of patients who overexpress this oncogene, indicating that HER-2/neu might be an appropriate target for immunotherapeutic development.

Smart mitochondria



Guy Perkins, UCSD, Terrence Frey, SDSU

How smart is a mouse? That might depend on its mitochondria, report Roubertoux *et al.* in the September *Nature Genetics*. The investigators found that mitochondrial DNA, in combination with nuclear DNA, can influence cognition.

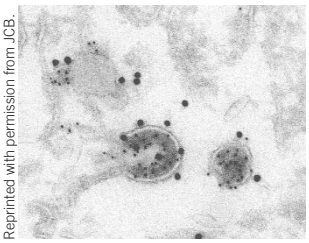
Many mitochondrial disorders, such as those that lead to stroke and epilepsy, affect the brain. This is not surprising, as mitochondria influence neuronal development and structure, as well as axonal and synaptic activity. But very little work has assessed how mitochondria affect cognition.

To address this question, the investigators created mice with nuclear DNA from one mouse strain and mitochondrial DNA from another. After this genetic feat, they tested cognition in mice with the dual sets of genes. The resulting mice performed poorly in tests of learning and memory, compared with mice with matching sets of mitochondrial and nuclear genomes. The difference between the two types of mice became more pronounced with age.

The mammalian mitochondrial genome contains only 13 genes that encode polypeptides, all of which take part in oxidative phosphorylation. The investigators suggest that these genes might modulate embryonic development of the central nervous system, as the less sharp mice seemed to have delayed sensory development shortly after birth. Otherwise the mice appeared normal, exhibiting no changes in maternal behavior or aggression. The study suggests that mothers, who pass on mitochondria, might wield even more influence than previously thought.

Charlotte Schubert and Pierrette Lo

HIV's inside passage



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In macrophages, one of the main targets of HIV-1, assembly of the virus occurs on the inside of the cell, report Pelchen-Matthews *et al.* in the 4 August *Journal of Cell Biology*. The strategy positions the viral particles to escape upon exocytosis, say the authors, and might give HIV-1 an infectious edge over the conventional mechanism of budding from the plasma membrane. HIV-1 takes the latter route when it emerges from $CD4^+$ T-helper cells, its other main target. Pelchen-Matthews determined exactly where the virions mature in macrophages. They visualized budding HIV-1 particles incorporating glycoproteins from late endosomes (immunolabeling shown here), consistent with observations by other groups. The investigators went on to provide evidence that the majority of viral particles take this interior exit route. It is unclear when infected macrophages release their deadly contents, but recent studies have suggested that another HIV-1 target, dendritic cells, seem to pass HIV-1 on during antigen presentation to T cells.

Sparing the heart

Thyroid hormones can counteract obesity by inducing weight loss, speeding up metabolism and reducing cholesterol. Because the hormones also ramp up heart rate, they are not used to treat obese individuals unless they also have thyroid disorders. In the 29 July online issue of *PNAS*, Grover *et al.* minimize the risks and maximize the benefits of activating thyroid hormone receptors. The authors examined the effects of selectively activating TR-β, one of two thyroid hormone receptors. TR-β controls cholesterol and metabolic rate, whereas TR-α controls heart rate. When they tested KB-141, a thyroid receptor agonist that activates TR-β but not TR-α, mice and rats experienced increased metabolism and reduced cholesterol. There were similar responses in primates, including weight loss—without increased heart rate or other unwanted effects. Although this work is in the early stages, the authors suggest that TR-β-selective chemicals could someday be used to lower weight and cholesterol without harming the heart.

Drug dilemma

Asthma researchers have begun to understand a paradox that plagues some of the most common asthma medications: they appear to exacerbate the disease in some frequent users. Drugs like Ventolin (albuterol) relax airways by stimulating β2-adrenergic receptors in smooth muscle cells. But heavy use can result in airway constriction. One hypothesis is that these drugs may, in the long term, downregulate β2-adrenergic receptors. In the 15 August *Journal of Clinical Investigation*, McGraw *et al.* suggest an alternate explanation. Based on experiments in transgenic mice either lacking the β2-adrenergic receptor or overexpressing it, the investigators report that long-term, high-level activation of the receptor leads to increased expression of phospholipase C-β. This molecule can promote muscle contraction by spiking calcium levels through an inositol triphosphate–containing pathway. Understanding the consequences of persistent β2-adrenergic receptor activation could lead to new drugs that avoid the negative effects of receptor activation.